IN THE UNITED STATES DISTRICT COURT
FOR THE EASTERN DISTRICT OF TEXAS
BEAUMONT DIVISION

IN RE NORPLANT CONTRACEPTIVE PRODUCTS LIABILITY LITIGATION	:	MDL DOCKET NO. 1038
	:	ALL CASES

No. 3

MEMORANDUM IN SUPPORT OF MOTION FOR PARTIAL SUMMARY JUDGMENT RE CONDITIONS FOR WHICH THERE IS NO EVIDENCE OF CAUSATION

INTRODUCTION

Now that the MDL plaintiffs have submitted verified interrogatory answers, the bizarre range of their complaints is on full view. Plaintiffs collectively claim that, as a result of their Norplant use, they suffered depression, strokes, pseudotumor cerebri, and a variety of other "exotic" conditions – more than 950 in number – including body odor, drug addiction, evil thoughts, finger nails changing color, loss of logical reasoning, stretch marks, tapeworms, toothache, and tuberculosis.[1] Even if plaintiffs are serious about tapeworms, toothache and tuberculosis, they do not contend that Norplant is the ***only*** possible cause of these conditions.

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[1] Attached at Tab 35 is a list, compiled from plaintiffs' verified interrogatory answers, of all the complained-about conditions. Not included in the list are the "core" conditions that are the subject of Motion Nos. 1 and 2, *Motion for Partial Summary Judgment Re The Learned Intermediary Doctrine/Proximate Cause* and *Motion for Partial Summary Judgment Re Adequacy of the Norplant Labeling* – with the following exception: six conditions are common to Motion Nos. 1, 2 and 3 – namely breast discharge, cervicitis, musculoskeletal pain, abdominal discomfort, leukorrhea, and vaginitis. These six are listed in the "Adverse Reactions" section of the physician labeling as being "possibly related" to Norplant. But because there is no scientific evidence of a statistically significant relationship between Norplant and these six conditions, they are included in the present motion as well.

For the purpose of this motion, the 950-plus complaints are referred to as the "exotic" conditions.

And, the same is true, of course, for the entire list of plaintiffs' alleged conditions: there are a number of potential causes for those conditions unrelated to Norplant. Plaintiffs' burden is to establish both (i) general causation – that Norplant ***can*** cause each of these alleged conditions and (ii) specific causation – that it did so in each of their individual cases. And plaintiffs must do so on the basis of scientifically reliable evidence.

This motion for partial summary judgment focuses on the first element of plaintiffs' burden. Because plaintiffs cannot come forward with scientifically reliable evidence of general causation – that Norplant can cause the "exotic" conditions – partial summary judgment is appropriate.

ARGUMENT

I. PLAINTIFFS MUST SUBMIT SCIENTIFICALLY RELIABLE EVIDENCE THAT NORPLANT CAUSES THE COMPLAINED-ABOUT CONDITIONS.

A. In the Absence of Scientifically Reliable Evidence of Causation, Wyeth is Entitled to Summary Judgment.

Summary judgment is appropriate, "after adequate time for discovery and upon motion, against a party who fails to make a showing sufficient to establish the existence of an element essential to that party's case, and on which that party will bear the burden of proof at trial." *Celotex Corp. v. Catrett*, 477 U.S. 317, 322 (1986) (upholding the district court's grant of summary judgment to defendant where plaintiff produced no evidence that her injuries were caused by defendant's asbestos product). "In such a situation, there can be no genuine issue as to any material fact, since a complete failure of proof concerning an essential element of [plaintiffs'] case necessarily renders all other facts immaterial." *Id.* at 322-23 (quotation omitted). Plaintiffs bear the burden of proving that Norplant is capable of causing each of the complained-about conditions. If plaintiffs can produce no admissible scientific evidence to support causation, Wyeth is entitled to summary judgment.

This Court has recognized before that Wyeth, in moving for summary judgment, may discharge its' burden of demonstrating that there is no genuine issue of material fact by showing that there is an absence of evidence to support an element of plaintiff's case. *See Memorandum Opinion and Order Denying Defendants' Motion for Partial Summary Judgment on Limitations Grounds* at 9 (February 21, 1997) (citing *Celotex*). Plaintiffs burden to produce evidence in support of their claim is not satisfied by "conclusory allegations ... unsubstantiated assertions ... or by only a 'scintilla' of evidence." *Little v. Liquid Air Corp.*, 37 F.3d 1069, 1075 (5th Cir. 1994) (en banc) (quotations omitted) (affirming grant of summary judgment to defendant manufacturer where plaintiff produced no evidence establishing a causal connection between the alleged defect in the warning and the injury suffered). Plaintiffs must adduce affirmative evidence, *see Memorandum Opinion and Order Denying Defendants' Motion for Partial Summary Judgment on Limitations Grounds* at 9 (February 21, 1997), specifically, affirmative evidence that an allegedly defective drug is capable of causing the complained-of conditions. *Fontenot v. Upjohn Co.*, 780 F.2d 1190 (5th Cir. 1986) (affirming grant of summary judgment to defendant manufacturer of progestin drug where plaintiff produced no evidence that progestin was capable of causing the complained-of heart defects).

B. *Daubert* Establishes the Requirements for Scientifically Reliable Admissible Evidence of Causation.

In order to establish that Norplant can cause each of the complained-about conditions, plaintiffs must present expert testimony that satisfies the requirements of *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579 (1993). Under *Daubert*, admissible expert testimony must be based on "scientific knowledge," that is, knowledge grounded in and based upon the "methods and procedures of science" and "supported by appropriate validation." *Id.* at 589-90. Invited to circumscribe *Daubert* in *Kumho Tire Co., Ltd. v. Carmichael*, 119 S. Ct. 1167 (1999), the Supreme Court instead broadened it, underscoring the importance of the district

court's "gatekeeping" obligation to "ensure that any and all scientific testimony ... is not only relevant, but reliable." *Id.* at 1174.

Both before and since *Daubert*, the courts have consistently defined what is scientifically reliable evidence of causation in pharmaceutical cases. In such cases, "the most useful and conclusive type of evidence ... is epidemiological studies." *Brock v. Merrell Dow Pharmaceuticals, Inc.*, 874 F.2d 307, 311 (5th Cir. 1989), *modified on reh'g*, 884 F.2d 166 (5th Cir. 1989) (plaintiff's failure to present statistically significant epidemiological proof of causation required dismissal); *Allen v. Pennsylvania Eng'g Corp.*, 102 F.3d 194, 197 (5th Cir. 1996) (where no epidemiological study has found a statistically significant link between the product and the alleged injury, expert testimony of an association does not meet the standard of reliability required under *Daubert* and the law of the Fifth Circuit). Although this Court has previously explained that Fifth Circuit law controls questions of federal law in this litigation, *see Memorandum and Order Granting Plaintiff's Motion to Remand, Doe, et. al. v. Wyeth-Ayerst Laboratories, et. al*, No. 1:94CV5006 (E.D. Tex. March 17, 1995) (following *In re Korean Air Lines Disaster of Sept. 1, 1983*, 829 F.2d 1171 (D.C. Cir. 1987), *aff'd*, 490 U.S. 122 (1989)), the Fifth Circuit is not alone in placing importance on epidemiological studies to prove causation. *See Raynor v. Merrell Pharmaceuticals, Inc.*, 104 F.3d 1371 (D.C. Cir. 1997) (affirming j.n.o.v. and exclusion of plaintiff's expert testimony because, among other reasons, experts' conclusions regarding causation were directly contradicted by the significant body of epidemiological data) (post-*Daubert*); *Daubert v. Merrell Dow Pharmaceuticals, Inc*, 43 F.3d 1311 (9th Cir. 1995) (rejecting plaintiffs' expert testimony as inadmissible under *Daubert*, noting that none of plaintiffs' experts could testify that the epidemiological data showed a relative risk of greater than two, and that relative risk of less than two actually tended to disprove legal causation) (post-*Daubert*); *In re Joint Eastern & Southern District Asbestos Litigation*, 52 F.3d 1124, 1128 (2d

Cir. 1995) ("[E]pidemiological evidence is indispensable in toxic and carcinogenic tort actions where the direct proof of causation is lacking.") (post-*Daubert*); *Turpin v. Merrell Dow Pharmaceuticals, Inc.*, 959 F.2d 1349 (6th Cir. 1990) (affirming grant of summary judgment for defendants because the evidence relied upon by plaintiffs, which did not include any published epidemiological studies, was insufficient basis for opinion on causation) (pre-*Daubert*); *Richardson v. Richardson-Merrell, Inc.*, 857 F.2d 823, 831 n.59 & 832 (D.C. Cir. 1988) (affirming j.n.o.v. for defendant drug manufacturer because none of the great wealth of epidemiological data found a statistically significant relationship; and "[i]n mass tort cases ... epidemiological studies are of critical significance") (pre-*Daubert*); *Hull v. Merrell Dow Pharmaceuticals, Inc.*, 700 F. Supp. 28 (S.D. Fla. 1988) (granting summary judgment for defendant because, as a matter of law, plaintiffs lack sufficient evidence to establish causation where no epidemiological data supports causation) (pre-*Daubert*).

This Court, too, has emphasized the importance of epidemiological evidence to prove that pharmaceutical products cause the conditions attributed to them. When the MDL bellwether plaintiffs sought to argue that Norplant causes mood changes (and at a rate ten times greater than in IUD users), Wyeth moved *in limine* to bar such argument, because there is no scientifically reliable evidence – *i.e.*, no statistically significant association established by epidemiological evidence – to support it. The Court granted Wyeth's motion, explaining that "[e]pidemiological data that is not 'statistically significant' cannot provide a scientific basis for an opinion on causation." *Order Granting Defendant's Motion in Limine to Bar Argument That the Incidence of Mood Changes Was Ten Times Higher in Norplant Users Compared to IUD Users* (Feb. 20, 1997) (citing *Allen*, 102 F.3d at 197).

That ruling applies equally to each of the "exotic" conditions, for there is ***no*** epidemiological data to link them to Norplant, much less statistically significant epidemiological data. *See Allen*, 102 F.3d 194.

C. There Is No Scientifically Reliable Evidence That Norplant Causes the "Exotic" Conditions.

Daubert requires that plaintiffs come forward with scientifically reliable evidence of general causation for each side effect before an expert witness will be permitted to testify at trial that Norplant caused their particular "exotic" injuries. Plaintiffs have not done so in any Norplant case to date, and with good reason: no such evidence exists.

To secure FDA approval for Norplant, the Population Council was required to conduct clinical trials of the product in accordance with federal regulations.[2] The Norplant clinical trials included two controlled studies—Study 01 and Study 21/25—that compared adverse effects reported by Norplant users to those reported by intrauterine device (IUD) users (the control group).[3] The trials showed no statistically significant difference in the risk of depression, stroke, or pseudotumor cerebri among Norplant users when compared with women using IUDs. Dr. Stephen Heartwell, an epidemiologist who currently serves as an associate professor in the Department of Obstetrics and Gynecology at the University of Texas Southwestern Medical School, has testified that there is no scientifically reliable evidence that Norplant causes these conditions or any others not listed in the labeling.

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2 The Population Council, a non-profit research organization, developed and tested Norplant and obtained FDA approval for its use in the United States. The Norplant clinical trials are epidemiological studies submitted in support of FDA approval. Affidavit of Stephen Heartwell, Dr.P.H., ¶ 4, Tab 33.

3 The two studies are "cohort" or "incidence" studies as described in *Merrell Dow Pharmaceuticals, Inc. v. Havner*, 953 S.W.2d 706, 721 (Tex. 1997), *cert. denied,* 118 S. Ct. 1799 (1998).

In describing Table Saf-19 of the New Drug Application, which summarizes the clinical trial findings as to non-menstrual side effects, Dr. Heartwell explained that "[t]here are no other conditions or adverse reactions beyond what is listed here in which a statistically significant association was found." Deposition of Stephen Heartwell, Dr.P.H. at 53, Tab 96. Table Saf-19 contains the only conditions other than bleeding irregularities – namely, headaches, nausea, dizziness, adnexal enlargement, dermatitis, acne, change in appetite, mastalgia, breast discharge, weight gain, and hair problems[4] – for which the clinical trials revealed any evidence of a statistically significantly higher percentage in Norplant users as compared to IUD users. Depression, stroke, pseudotumor cerebri and the more than 950 "exotic" conditions are ***not*** on the list. Dr. Elizabeth L. Vliet, one of plaintiffs' experts in the first bellwether trial, when asked in a subsequent case whether she could identify any controlled studies that showed a statistically significant increased risk of depression among Norplant users compared to any control group, answered that she could not identify even one such study.[5] *See* Deposition of Dr. Elizabeth Vliet at 192-206, Tab 98.[6] ***None*** of the "exotic" conditions has been found to be statistically

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4 The results of the Norplant controlled clinical trials are summarized in a table in Tab 43. The table is derived from the clinical trial data included in the Norplant New Drug Application, Table Saf-19, Tab 44.

5 *See* Heartwell Depo. at 62, Tab 93 ("There was no scientific evidence in terms of an association between the use of Norplant and depression in the clinical trials."). In fact, the data collected in the Norplant trials revealed that depression was *more common in IUD users than Norplant users*. *See id.* (referring to Table 2Saf-9, Tab 45).

6 Even had she been able to name one, an isolated study showing an increased risk does not suffice to establish causation, particularly where the study does not satisfy the factors of the strength and consistency of the association are weak. *See Kelley v. American Heyer-Shulte Corp.*, 957 F. Supp. 873 (W.D. Tex. 1997) (it would be unreasonable as a matter of law to rely on a single study showing a statistically significant association to establish a causal link where the observed association was neither strong nor consistent); *see also Havner*, 953 S.W.2d at 727 ("an isolated study finding a statistically significant association between Bendectin and limb reduction defects would not be legally sufficient evidence of causation").

significantly associated with Norplant use in the two controlled clinical studies reported in the Norplant NDA. Heartwell Aff., ¶¶ 9-11, 13, Tab 33.

Nor have these "exotic" conditions been found to be statistically significantly associated with Norplant use in ***any*** published scientific study relied on by plaintiffs' experts. Dr. Heartwell has reviewed the approximately 64 articles from the medical literature upon which plaintiffs' experts purportedly rely, and he concludes:

> None of these articles report any controlled epidemiological studies that show a statistically significant association between Norplant use and any of the side effects listed in Exhibit C or an increased risk of any of the side effects listed in Exhibit C in women using Norplant or in Norplant users compared to any control group.
>
> Based on the scientific and clinical data from the Norplant Phase III controlled clinical trials, as well as my review of the medical literature relied on by plaintiffs' experts, *it is my opinion that there is no reliable scientific evidence that Norplant can cause any of the side effects listed on Exhibit C, or even that Norplant creates an increased risk of these conditions.*

Heartwell Aff., ¶¶ 12-13 (emphasis added).[7]

The lack of studies is not the product of Norplant being a drug too new to be studied. During the 20 years that it was being developed, Norplant received considerable scientific scrutiny. Even before FDA approval in 1990, more than 300 articles about Norplant had been published in the scientific literature; since approval, at least another 660 articles. *See* Tabs 39 & 40. Moreover, the sole active ingredient in Norplant – the hormone, levonorgestrel – has been used in contraceptives for more than 25 years and has been the subject of countless additional articles in the medical literature. The scientific status of Norplant, then, is not that there is no evidence of causation because the active ingredient is new or an inadequate number of

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[7] Exhibit C to Dr. Heartwell's Affidavit corresponds to the list of "exotic" conditions at Tab 35.

studies have been done. Rather, countless studies have been completed in addition to the clinical trials, and they offer no scientific support for the proposition that Norplant can cause the alleged "exotic" conditions. Heartwell Aff., ¶¶ 13, 14-17, Tab 33.

In the event that plaintiffs now come forward with evidence that they claim supports an association between Norplant and any of the "exotic" conditions, Wyeth requests a *Daubert* hearing in order to challenge the scientific basis for any such opinion.[8] The same group of experts have been trotted out by plaintiffs in this litigation – both in the MDL and in various state court proceedings – time after time.[9] None of them have any significant experience with Norplant, none of them have conducted any studies of Norplant, none have tested it, none have written in the peer-reviewed literature about it, and none of them have testified before that Norplant causes this encyclopedia of "exotic" conditions. There is no reason to believe that any one of them will be able to offer an opinion on general causation that passes muster under *Daubert*.[10]

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8 When a motion for summary judgment is opposed by expert testimony, the court should inquire into the reliability and foundation of any proposed opinion to determine its admissibility. *Washington v. Armstrong World Industries, Inc.*, 839 F.2d 1121, 1122-23 (5th Cir. 1988) (upholding the district court's exclusion of plaintiff's expert's testimony as "pure speculation and fundamentally unreliable" and affirming grant of summary judgment).

9 The MDL plaintiffs designated Dr. Dennis Mazur, Dr. Bruce Sales, Peter Carpenter, Dr. Edward Gripon, Dr. Anthony Lucci, Dr. John Haynes, and Dr. Elizabeth Vliet, and one or more of these same experts have been designated in state cases in Alabama, Indiana, New York, and Texas.

10 *See Memorandum in Support of Defendant's Motion to Exclude Expert Testimony*, (Jan. 28, 1997).

CONCLUSION

Plaintiffs have not and cannot produce any scientifically reliable evidence that Norplant can cause the 950 or more "exotic" complaints. In the absence of such evidence, partial summary judgment should be granted against ***all*** plaintiffs on ***all*** such claims. Ridding the litigation of these spurious allegations will dramatically narrow its scope.

Respectfully submitted,

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Dated: May 24, 1999

CERTIFICATE OF SERVICE

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